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Morphological and Functional Changes in Retinal Vessels Associated with Branch

Retinal Vein Occlusion

Running head: Changes in Retinal Vessels due to BRVO

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Abstract

Objective: To study the morphological and functional changes in retinal veins of eyes affected with branch retinal vein occlusion (BRVO) by thin sectioning with optical coherence tomography (OCT).

Design: Prospective, observational, cross-sectional study.

Participants: Twenty-five consecutive patients (25 eyes) with acute BRVO.

Methods: Major retinal veins, arteries, and arteriovenous (A/V) crossing were examined by sequential thin sectioning by Spectralis HRA+OCT. The retinal blood flow was mimicked *in vitro* and was scanned with Spectralis HRA+OCT.

Main Outcome Measures: Morphological characteristics of normal and BRVO-affected retinal vessels seen in OCT sections.

Results: Cross-sectional OCT images revealed physiological retinal vessels as oval-shaped configurations with 4 distinctive hyperreflectivities in a line. The vessel walls showed the innermost and outermost hyperreflectivity, and the blood flow showed internal paired hyperreflectivities with an hourglass-shape. No eye with disturbed blood flow due to BRVO showed this internal hyperreflectivity pattern. *In vitro*, OCT sections of the blood within the glass tube without flow showed homogeneous reflectivities. Increased blood flow velocity resulted in the development of heterogeneous internal

reflectivity and hourglass-shaped hyperreflectivities. In all eyes with acute BRVO, sequential sectioning with OCT visualized three-dimensional vascular architecture as well as the intravascular conditions at the A/V crossing. At the affected A/V crossing, arterial overcrossing was seen in 17 eyes and venous overcrossing was seen in 8 eyes. In eyes with arterial overcrossing, the retinal vein seemed to run deep under the artery at the A/V crossing, and the venous lumen often appeared to be preserved even at the A/V crossing. In all eyes with venous overcrossing, the retinal vein appeared to be compressed and choked between the internal limiting membrane and the arterial wall at the A/V crossing. OCT sectioning showed intravenous thrombi in 21 eyes, and the thrombi were detected downstream of the A/V crossing in all the cases. The detection of thrombus was significantly associated with ischemic pattern in BRVO ($P = 0.036$).

Conclusion: In eyes with BRVO, sequential thin sections with OCT visualized three-dimensional retinal vasculature. Present OCT findings suggest that BRVO may occur by 2 different mechanisms, depending on the relative anatomical positions of crossing vessels.

1 Branch retinal vein occlusion (BRVO) is the second most common retinal vascular
2 disorder after diabetic retinopathy. BRVO is defined as focal occlusion of the major
3 retinal vein, occurring most frequently at an arteriovenous (A/V) crossing.^{1, 2} Acute
4 BRVO is characterized by flame-shaped retinal hemorrhage and venous dilation and
5 tortuosity in the affected retina, often with macular edema. However, the precise
6 pathogenesis of BRVO is unclear. Previous histological studies have suggested that the
7 major artery and vein share a common adventitial sheath at the A/V crossing and that the
8 mechanical compression of rigid arterial walls causes narrowing of the venous lumen,
9 resulting in flow disturbance at the A/V crossing.³⁻⁵ A subsequent study with fluorescein
10 angiography (FA) reported that most of the eyes affected with BRVO showed venous
11 lesions downstream of the affected A/V crossing.⁶ The hemodynamic changes
12 downstream of the A/V crossing were suggested to be important in the occurrence of
13 BRVO, which predisposes the eye to endothelial damage and thrombus generation.^{6, 7}

14 Technological advances in imaging resolution and acquisition speed of optical
15 coherence tomography (OCT) have enabled observation of the retinal architecture in
16 greater detail and have contributed to our understanding of the pathomorphology of
17 various macular diseases. Recent extensive investigations with OCT have
18 demonstrated the morphological changes associated with BRVO, including foveal cystoid

spaces,^{8, 9} serous retinal detachment,^{10, 11} hyperreflective foci,¹² and subretinal
hemorrhage.^{13, 14} In addition, OCT investigations revealed the importance of the outer
aspect of the foveal photoreceptor layer in the visual functions of eyes with BRVO.^{9, 15-17}
Based on these findings, OCT may have the potential to elucidate the morphological
changes and functional alterations in retinal veins affected with BRVO. To date,
however, little information is available on the OCT features of retinal vasculature.¹⁸⁻²⁰
This study aimed to elucidate the pathogenesis of BRVO and investigate the clinical
relevance of the morphological changes of retinal vasculature in BRVO by studying the
morphological changes of BRVO-affected retinal veins by sequential thin sectioning with
OCT.

PATIENTS AND METHODS

Patients

This prospective study consisted of 25 consecutive patients (25 eyes) with unilateral acute major BRVO who were examined at the Department of Ophthalmology of Kyoto University Hospital between August 2011 and March 2012. The duration of symptoms in all the eyes was less than 6 months. BRVO was diagnosed on the basis of fundus examination and FA findings of 2 retina specialists (AT, TM). Eyes with BRVO in which the occluded site of the retinal vein was located within the optic disc or on the disc margin were not included in the current study. Eyes with central retinal vein occlusion (CRVO), co-existing ocular disease (i.e., glaucoma, diabetic retinopathy, or senile cataract that resulted in poor-quality OCT images) were also excluded. In addition to the study subjects, 9 patients (9 eyes) with old BRVO, in which the retinal hemorrhage had been completely absorbed, and 1 patient (1 eye) with hemi-CRVO were also examined to confirm the correlations between perfusion status obtained with FA and OCT findings. The Institutional Review Board and the Ethics Committee of Kyoto University approved this study. The study protocol adhered to the tenets of the Declaration of Helsinki. A written informed consent for the study participation was obtained from each patient.

After comprehensive ophthalmic examinations, including the measurement of

best-corrected VA in a Landolt chart and fundus biomicroscopy with a non-contact lens, 45° digital fundus photographs were obtained using a digital fundus camera (TRC-50LX, Topcon, Tokyo, Japan; 3,216 × 2,136 pixels) after pupil dilatation. To assess the retinal perfusion status, each patient underwent FA with a confocal laser scanning system (HRA-2, Heidelberg Engineering, Heidelberg, Germany). Eyes with BRVO were classified as ischemic when the area of nonperfusion was greater than 5 disc diameters in size.

We assessed major retinal vessels within the retina affected with BRVO in detail using sequential thin sectioning with Spectralis HRA+OCT (Heidelberg Engineering). Sequential longitudinal sections were made along the major retinal veins or arteries (minimally 25 sections of 5°). Sequential cross-sections were made vertical to each major retinal vessel. Each section was averaged with at least 20 scans obtained at the same location. The affected A/V crossing was also examined with sequential longitudinal and cross-sections.

OCT examinations of blood flow *in vitro*

To mimic the retinal blood flow *in vitro*, we used fine glass tubes approximately 200 μm in diameter. Human blood was extracted from healthy volunteers and heparinized. A fine

1 glass tube was connected to a pump to circulate the extracted human blood at arbitrary
2 flow rates. Cross-sections of the blood flowing within the tube were scanned using
3 Spectralis HRA+OCT. A 25-diopter lens was attached to an OCT machine to adjust the
4 focus on the blood flow within the glass tube. Each image was obtained using an
5 average of 20 scans. Previous studies have shown that the flow velocity in the major
6 retinal vessels of healthy eyes is approximately 5–35 mm/s.²¹ To cover the physiological
7 and pathological flow velocity, the flow rate (blood velocity) in the glass tube was
8 gradually increased from 0–10.0 ml/h (0–88.4 mm/s).

9

10 **Statistical Analysis**

11 Statistical analysis was performed using PASW Statistics version 18.0 (SPSS, Chicago,
12 IL). Values are presented as mean \pm standard deviation. For statistical analysis, VA
13 measured with a Landolt chart was converted to a logarithm of the minimum angle of
14 resolution (logMAR). Student's *t* test was used to compare quantitative data with normal
15 distributions and equal variance. Significant differences in the sampling distributions
16 were determined using the chi-square test. A *P* value of less than 0.05 was considered
17 to be statistically significant.

RESULTS

OCT imaging of normal retinal vessels

To study the OCT features of retinal vasculature, we first examined the major retinal vessels in the healthy contralateral eyes. Cross-sectional OCT images revealed major retinal vessels as oval-shaped configurations with heterogeneous reflectivities, mainly in the retinal nerve fiber layer and occasionally in the inner plexiform layer (IPL) (Fig. 1). In cross-sections, physiological vessels showed 4 distinctive hyperreflectivities in a line. The top and bottom of the vessel walls, which were vertical to the OCT light source, showed the innermost (vitreous side) and outermost (retinal pigment epithelium (RPE) side) hyperreflectivities. The arterial walls generally had higher reflectivity as compared to the venous walls. All retinal vessels with physiological blood flow showed inside paired hyperreflectivities, which was frequently hourglass-shaped (Fig. 1). The internal paired hyperreflectivities showed a double “c” pattern when the blood flow converged from 2 different veins (right vein shown in Fig. 1C).

Figure 2 ([available at http://aaojournal.org](http://aaojournal.org)) shows the longitudinal OCT sections of the major retinal vessels. Consistent with the cross-sections of the major retinal vessels, retinal vessels had 4 hyperreflective bands, of which the innermost and outermost bands were derived from the vessel walls and the 2 intermediate bands were derived from the

bloodstream.

Correlations between retinal blood flow in FA and OCT findings

To investigate whether the internal paired hyperreflectivities observed in the physiological retinal vessels are derived from the retinal blood flow, 9 eyes with old BRVO were examined with Spectralis HRA+OCT. The OCT images of the sheathed veins associated with old BRVO were then compared with the blood flow seen in FA. While blood flow was detected in the sheathed veins of 4 eyes, there was no blood flow in the sheathed veins of 5 eyes. In OCT sections of sheathed retinal veins with no blood flow, no internal paired hyperreflectivities were present (Fig. 3, [available at http://aaojournal.org](http://aaojournal.org)). However, paired hyperreflectivities were detected in all 4 eyes with blood flow in the sheathed veins.

OCT features of the blood flow *in vitro*

Figure 4 shows a fundus photograph and FA of a case of acute hemi-CRVO. In FA, physiological blood flow is seen in the lower vein but the blood flow of the affected upper vein is markedly disturbed. OCT cross-sections revealed internal paired hyperreflectivities within the walls of the lower unaffected vein but homogeneous

reflectivity without paired hyperreflectivities in the obstructed upper vein.

To mimic the blood flow in the major retinal vessels *in vitro*, we pumped blood samples through a fine glass tube at arbitrary flow velocities. Cross-sectional images of human blood flowing within the tube were obtained with Spectralis HRA+OCT. Figure 5 ([available at http://aaojournal.org](http://aaojournal.org)) shows the OCT images of the blood flowing through the fine glass tube at different flow velocities. OCT sections of the blood within the glass tube without flow (at 0 mm/s) showed no paired hyperreflectivities. However, increased blood flow velocity resulted in the development of heterogeneous internal reflectivity and hourglass-shaped hyperreflectivities within the glass tube.

Retinal vasculature changes associated with acute BRVO

To investigate the changes in retinal vasculature associated with BRVO, 25 eyes of 25 patients (13 women and 12 men) with acute BRVO were examined with Spectralis HRA+OCT (Table 1). Fundus examinations revealed retinal hemorrhage in all eyes, and venous dilation and tortuosity in the affected retina. In all eyes, FA showed filling delay in the affected vein but confirmed the blood flow at its late phase. OCT cross-sections revealed paired hyperreflectivities in the unaffected retinal veins of all eyes. However, none of the 25 eyes with BRVO showed this pattern of internal hyperreflectivities around

the affected A/V crossing.

It is sometimes difficult to determine the relative anatomical positions between the artery and vein at the affected A/V crossing using fundus examination alone. In 3 of 25 eyes, even FA could not elucidate the relative anatomical position at the affected A/V crossing. However, sequential thin sections of OCT clearly showed this association in all 25 eyes. At the affected A/V crossing of our patients, arterial overcrossing was seen in 17 eyes, while venous overcrossing was seen in 8.

In all eyes with acute BRVO, venous dilation and tortuosity were detected by fundus examinations. Three-dimensional venous tortuosity and the condition of the venous lumen at the affected A/V crossing could be visualized by sequential longitudinal and cross-sections analyzed by Spectralis HRA+OCT. In the eyes with BRVO of the artery overcrossing, OCT findings revealed that the retinal vein ran deep under the artery at the A/V crossing (Fig. 6). Of 17 eyes with arterial overcrossing, the venous wall remained in the inner nuclear layer (INL) and the outer plexiform layer (OPL) in 6 eyes (35.3%) and in the outer nuclear layer (ONL) in 8 eyes (47.1%). In 3 eyes (17.6%), tortuous retinal veins appeared to extend beyond the external limiting membrane (ELM) line and approaching RPE. The distance between the deepest edge of the venous wall and RPE ranged from 36–314 (mean: 139.6 ± 60.0) μm . In addition, OCT revealed that the

venous lumen was generally preserved even at the A/V crossing. In contrast, in all eyes with BRVO of the vein overcrossing, the affected vein appeared to be compressed and choked between internal limiting membrane (ILM) and the arterial wall at the crossing (Fig. 7).

In eyes with acute BRVO, OCT examination often showed thrombus formation around the affected A/V crossing. Thrombi were detected in 14 of 17 eyes with arterial overcrossing (82.3%) (Fig. 8, [available at http://aaojournal.org](http://aaojournal.org)), and in 7 of 8 eyes with venous overcrossing (87.5%) (Fig. 7). In 19 eyes, thrombus was seen from the A/V crossing to the downstream (Fig. 7, Fig. 8, [available at http://aaojournal.org](http://aaojournal.org)). In 2 eyes, the thrombi appeared to extend on both sides of the affected A/V crossing. None of the eyes showed thrombi only at the crossing site or upstream from the site.

To determine the clinical relevance of thrombus formation, we evaluated its association with clinical parameters (i.e., VA, foveal pathomorphology, and perfusion status) (Table 2). The presence of thrombus was significantly correlated with the perfusion status (ischemic BRVO) ($P = 0.036$, chi-square test), and marginally correlated with the height of foveal detachment ($P = 0.083$, Student's t test) and duration from the onset of symptoms ($P = 0.070$, Student's t test).

DISCUSSION

In cross-sectional OCT images of healthy eyes, major retinal vessels are observed as oval-shaped configurations with heterogeneous reflectivities, often with 4 distinctive hyperreflectivities in a line. The innermost and outermost hyperreflectivities are interpreted to be derived from the vessel wall because the top and bottom of the vessel walls are vertical to the OCT light source. All the vessels with physiological blood flow show inside paired hyperreflectivities, which were frequently hourglass-shaped and occasionally present in a double “c” pattern in convergent veins. However, no veins without blood flow showed this feature. In addition, as shown in Figure 4 of a case of acute hemi-CRVO, the vein with disturbed blood flow showed homogeneous reflectivity without this feature. Therefore, we hypothesized that this intravascular feature is a hallmark of the physiological blood flow.

To mimic the blood flow in the retinal vessels *in vitro*, we pumped blood samples through a fine glass tube at various flow velocities (Fig. 5, [available at http://aaojournal.org](http://aaojournal.org)). The cross-section of the glass tube without blood flow showed homogeneous internal reflectivity. Increased blood flow velocity led to the development of heterogeneous internal reflectivity and hourglass-shaped hyperreflectivities. According

to previous reports with bidirectional laser Doppler velocimetry, the blood velocity is 7–35 mm/s in the major retinal arteries and 5–25 mm/s in the major retinal veins.²¹ With unphysiological blood flow velocity (88.4 mm/s), however, this feature disappeared and the internal reflectivity was only observed at the anterior part of the lumen. When applying the theory of rheology to the major retinal vessels, the central stream has the maximal velocity; this was confirmed by Doppler OCT examinations, which revealed this distribution of the intravascular flow velocity.²²⁻²⁴ However, it remains to be elucidated why OCT sections of the retinal vessels with physiological blood flow show this feature. It must be noted that this feature can be observed even if other OCT devices are used (data not shown); this feature is not unique to Spectralis HRA+OCT alone.

Most cases of BRVO occur at A/V crossing sites.^{4, 25-28} It has been suggested that the large artery and vein share a common adventitial sheath at the A/V crossing. Hypertension, arteriosclerosis, and old age are risk factors of BRVO.^{1, 2, 25} The mechanical compression of rigid arterial walls has been suggested to cause narrowing of the venous lumen, resulting in the concomitant flow disturbance at the A/V crossing. In a histopathological study conducted by Frangieh et al.,³ all eyes with BRVO had fresh or recanalized thrombi in the affected vein with varying degrees of arteriosclerosis of the corresponding arteries. However, the cases investigated in their study were obtained

after 8 months to 12 years after the onset of BRVO; furthermore, 6 of the 8 specimens were obtained after the patients' death. In contrast, sequential thin sectioning of OCT facilitates three-dimensional analysis of the retinal vasculature in the acute phase of BRVO *in vivo* and elucidates the morphological changes as well as functional alterations in the affected retinal veins.

Fundus examination revealed venous dilation and tortuosity in all eyes with acute BRVO. OCT examinations revealed that venous tortuosity was more prominent in the sagittal direction. In this study, the affected vein appeared to extend beyond the ELM line, approaching the RPE lines in 3 eyes (17.6%). Because Müller cells spread their cell body from ILM to ELM and support the retinal architecture,^{29, 30} the elongated retinal veins in the eyes with BRVO may preferentially produce tortuosity in the sagittal direction than in the frontal direction.

Previous clinical studies have reported that 85–100% of BRVO occurs at the arterial overcrossing.^{3-7, 28, 31, 32} Sequential thin sectioning with OCT allowed detailed anatomical correlation between the artery and vein, revealing that BRVO occurred at the arterial overcrossing in 17 of the eyes (68%) investigated. Unexpectedly, OCT sections of these eyes showed that the retinal vein runs deep below the artery and that the venous lumen appears to be preserved at the A/V crossing. Our OCT findings are consistent

with a previous histological report on normal eyes.⁵ Jefferies et al. reported that sharp bending of the veins are frequently seen at the A/V crossing without compression and that focal narrowing of the veins are rarely seen at the A/V crossing in normal eyes.⁵

Recently, A/V sheathotomy has been reported as a treatment option for macular edema associated with BRVO.^{26, 33-35} Horio et al.³⁵ reported that A/V sheathotomy led to transient improvement of the retinal blood flow but this improvement subsided at 1 month. Although thrombi were occasionally observed to flow away through the affected vein during the surgery, the effect of dissection of the common sheath would limit the improvement in the circular disturbance. Mechanical compression of the artery may play a less important role in the pathogenesis of BRVO at the arterial overcrossing site. Rather, hemodynamic changes downstream of the A/V crossing may be essential in the pathogenesis of BRVO.

Unexpectedly, current OCT examinations showed that BRVO occurred at the venous overcrossing in 8 of the 25 eyes studied. In contrast to BRVO at the arterial overcrossing, OCT revealed that the affected veins were compressed and choked between ILM and the arterial wall at the venous overcrossing. At the venous overcrossing, the mechanical compression caused by the ILM and the arterial walls at the crossing would be primarily related to the onset of BRVO. To the best of our knowledge,

1 however, limited information is available on the pathophysiology or clinical information of
2 eyes with this pattern of BRVO. Previous histological studies have reported that no
3 focal venous narrowing was present at the venous overcrossing in normal eyes and that
4 veins may deviate towards the vitreous.⁵ For the treatment of BRVO at the venous
5 overcrossing, it is difficult to perform A/V sheathotomy, but ILM peeling including the
6 affected A/V crossing might effectively reduce the compression of the venous lumen.

7 Previous histological reports have demonstrated thrombus formation in the veins
8 affected with BRVO.^{3, 4} However, in a previous report with FA, thrombus formation was
9 detected in 7% of eyes with BRVO, always downstream of the affected A/V crossing.⁶ In
10 the current study, thrombi were detected in 14 of 17 eyes with arterial overcrossing, and
11 in 7 of 8 eyes with venous overcrossing. Thrombi were always detected downstream of
12 the A/V crossing, and no eye showed thrombus only at the crossing site or upstream of
13 the A/V crossing alone. Compared with the FA or fundus examination, sequential thin
14 sectioning with OCT is a more sensitive technique to visualize the thrombus in the
15 affected retinal veins. However, Seitz³⁶ described histological findings of a case with
16 BRVO a few hours after its onset: no blood thrombus obliterated the venous lumen at the
17 A/V crossing. It remains unclear whether intravenous thrombus formation is a cause or
18 consequence of BRVO.

1 There are some limitations of this study, mainly the small sample size and
2 cross-sectional study design. In addition, we must acknowledge that due to the dense
3 retinal hemorrhage or edema, it is sometimes difficult to analyze the distal side of the A/V
4 crossing in detail. We showed the morphological and functional changes in the retinal
5 vasculature at the A/V crossing in eyes with BRVO (i.e., anatomical positions of crossing
6 vessels and thrombus formation and the degree of venous tortuosity and flow condition).
7 However, most of our findings were descriptive and not quantitative. Despite these
8 shortcomings, the current OCT findings suggest that BRVO would occur from 2 different
9 mechanisms, depending on the relative anatomical positions of crossing vessels. In
10 addition, we detected a clinical relevance in the presence of thrombus in eyes with acute
11 BRVO, which were significantly correlated with the retinal perfusion status (ischemic
12 BRVO). This is a small case series; therefore, OCT studies with larger sample
13 populations would be necessary to elucidate the clinical relevance of the retinal
14 vasculature of BRVO.

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Table 1. Characteristics of patients with acute branch retinal vein occlusion

Age (years)	66.3 ± 11.9
Gender (women/men)	13/12
Duration of symptoms until examination (weeks)	10.0 ± 7.1
Visual acuity (logMAR)	0.33 ± 0.32
Foveal thickness (μm)	577.6 ± 220.5
Foveal cystoid spaces	23 (92%)
Hemorrhage within foveal cystoid spaces	18 (72%)
Foveal serous retinal detachment	16 (64%)
Foveal subretinal hemorrhage	12 (48%)
Retinal perfusion status (nonischemic/ischemic)	13/12

logMAR = logarithm of minimal angle of resolution.

Table 2. Comparisons of optical coherence tomography findings between 2 groups classified by the presence or absence of thrombus in the affected veins

	Thrombus (+)	Thrombus (−)	<i>P</i> value
Visual Acuity (logMAR)	0.38 ± 0.34	0.15 ± 0.12	0.210
Duration of symptoms (weeks)	11.1 ± 7.2	4.1 ± 1.6	0.070
Foveal thickness (μm)	592.4 ± 233.7	500.3 ± 124.8	0.456
Height of serous retinal detachment (μm)	155.2 ± 126.8	37.3 ± 43.1	0.068
Foveal cystoid spaces (+/−)	18/3	4/0	0.420
Hemorrhage within foveal cystoid spaces (+/−)	15/6	3/1	0.884
Foveal serous retinal detachment (+/−)	14/7	2/2	0.524
Foveal subretinal hemorrhage (+/−)	11/10	4/0	0.315
Retinal perfusion status (nonischemic/ischemic)	9/12	4/0	0.036

logMAR = logarithm of the minimum angle of resolution.

Figure1

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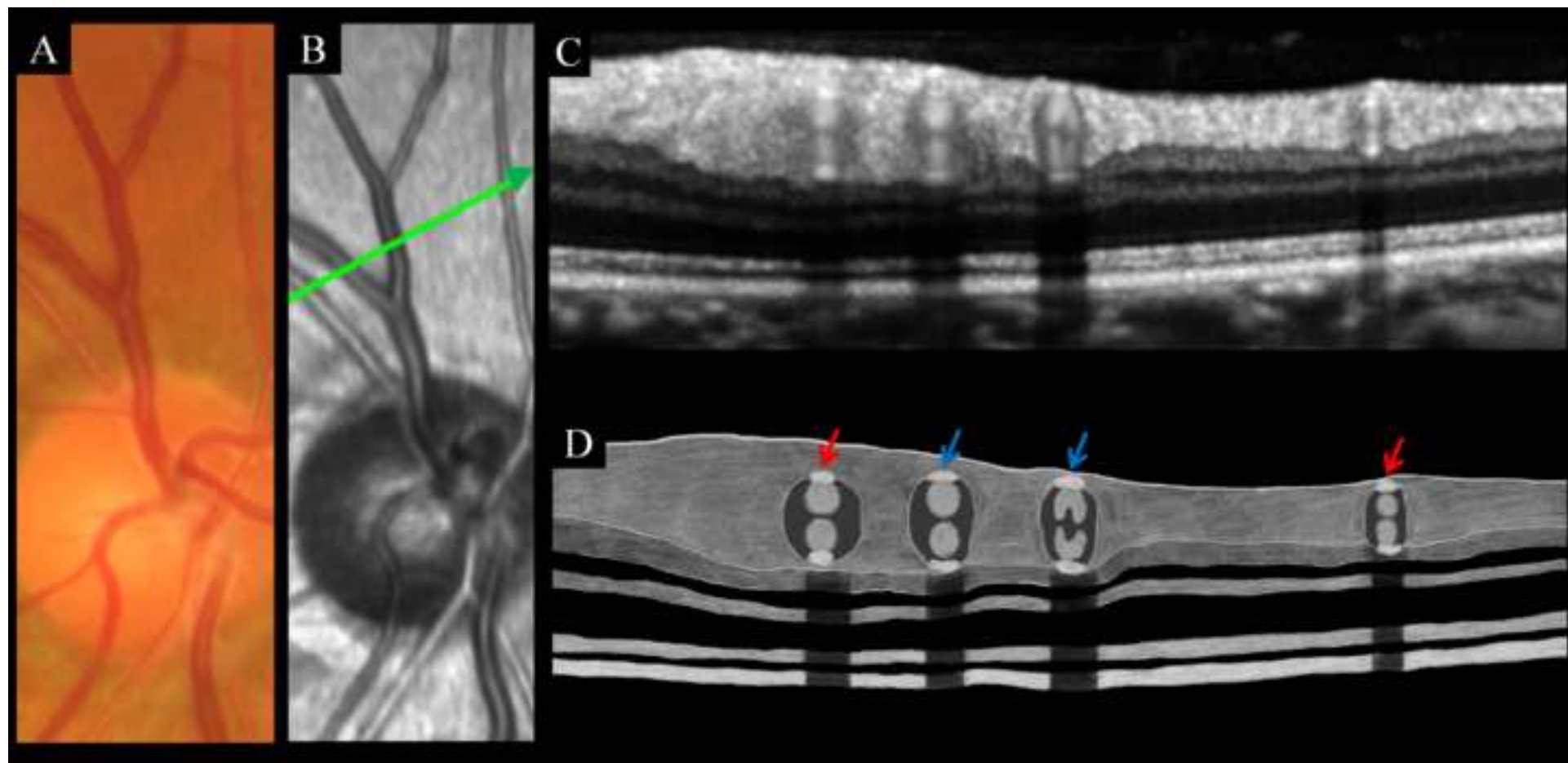
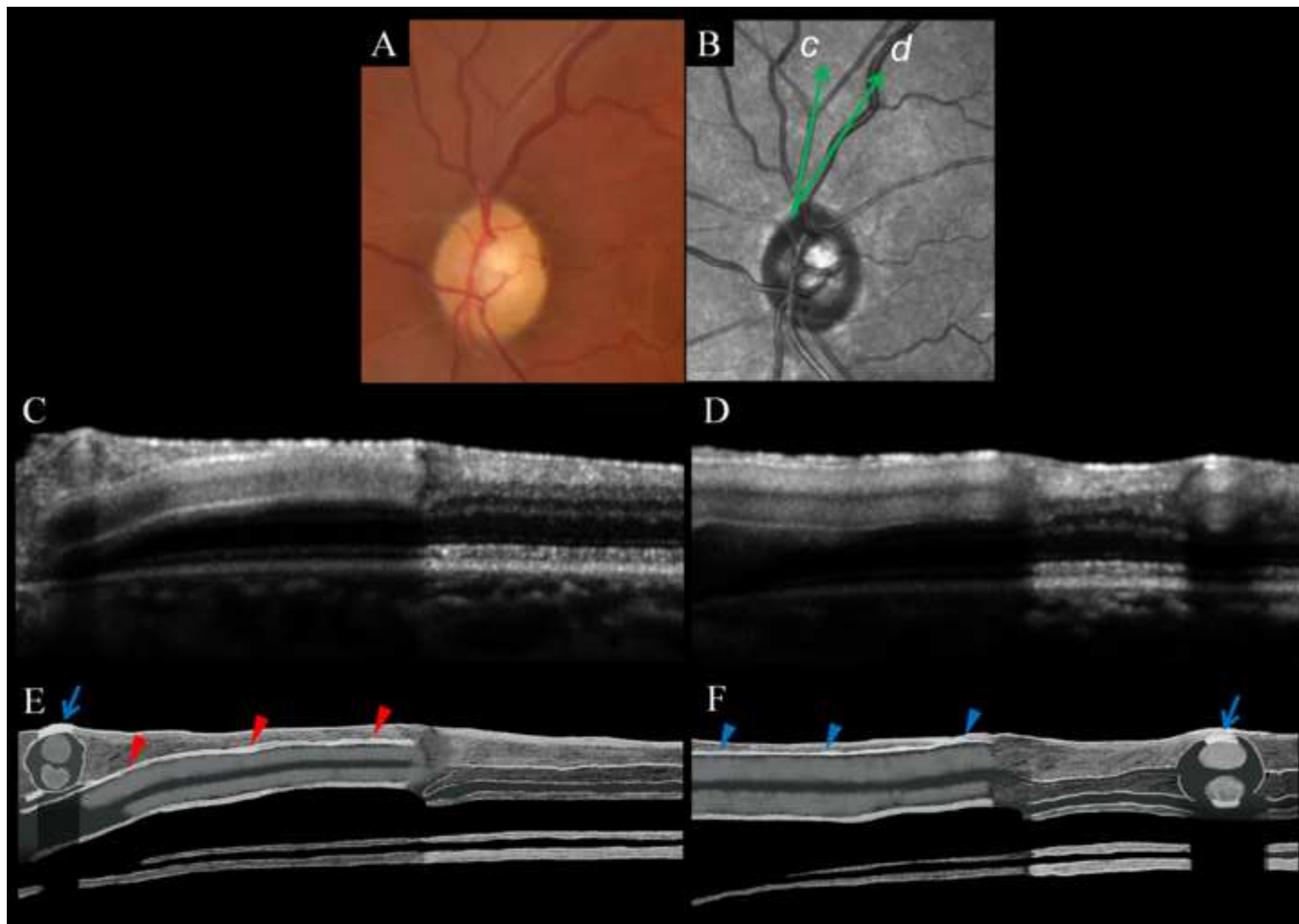


Figure2

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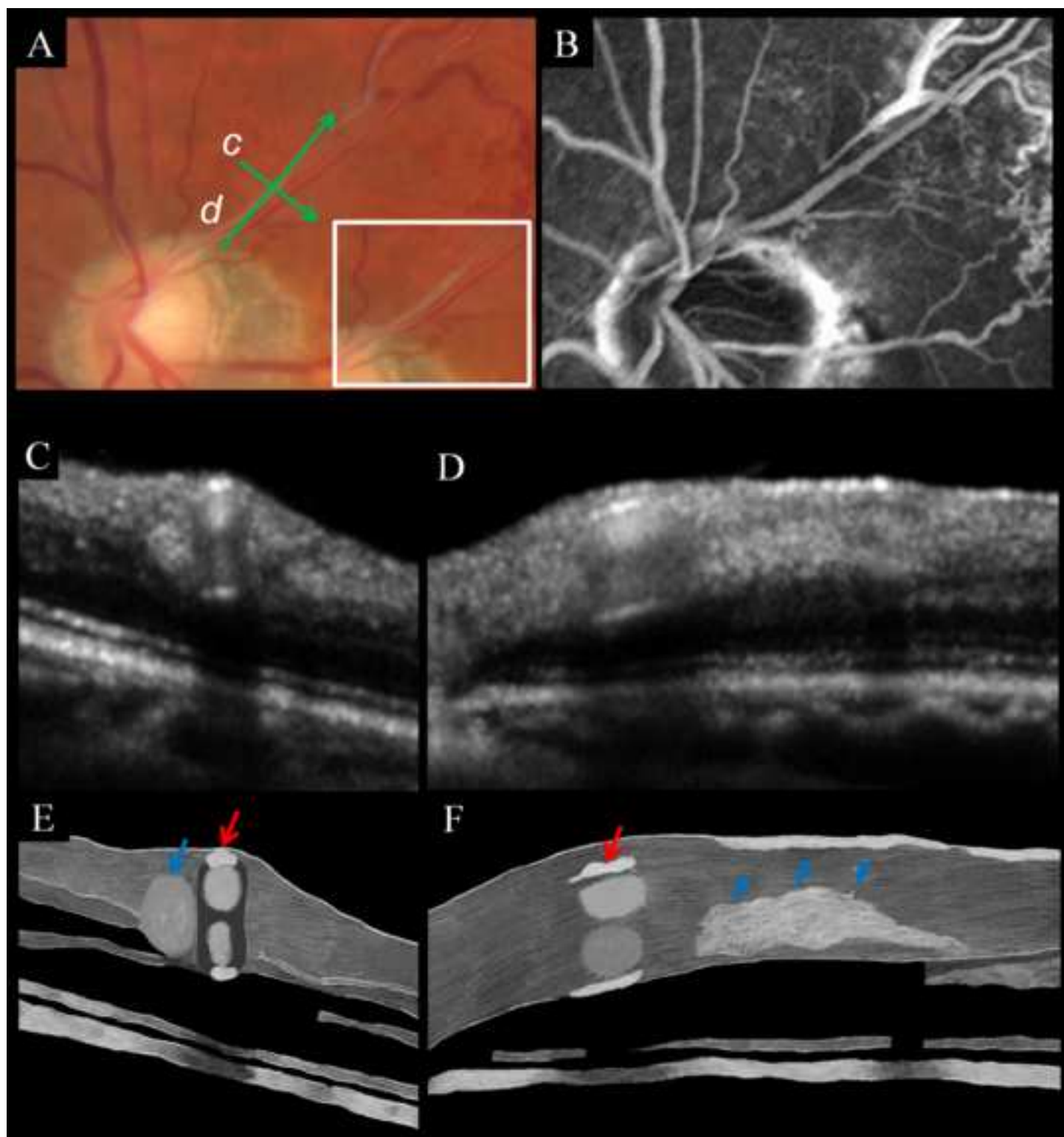


Figure4
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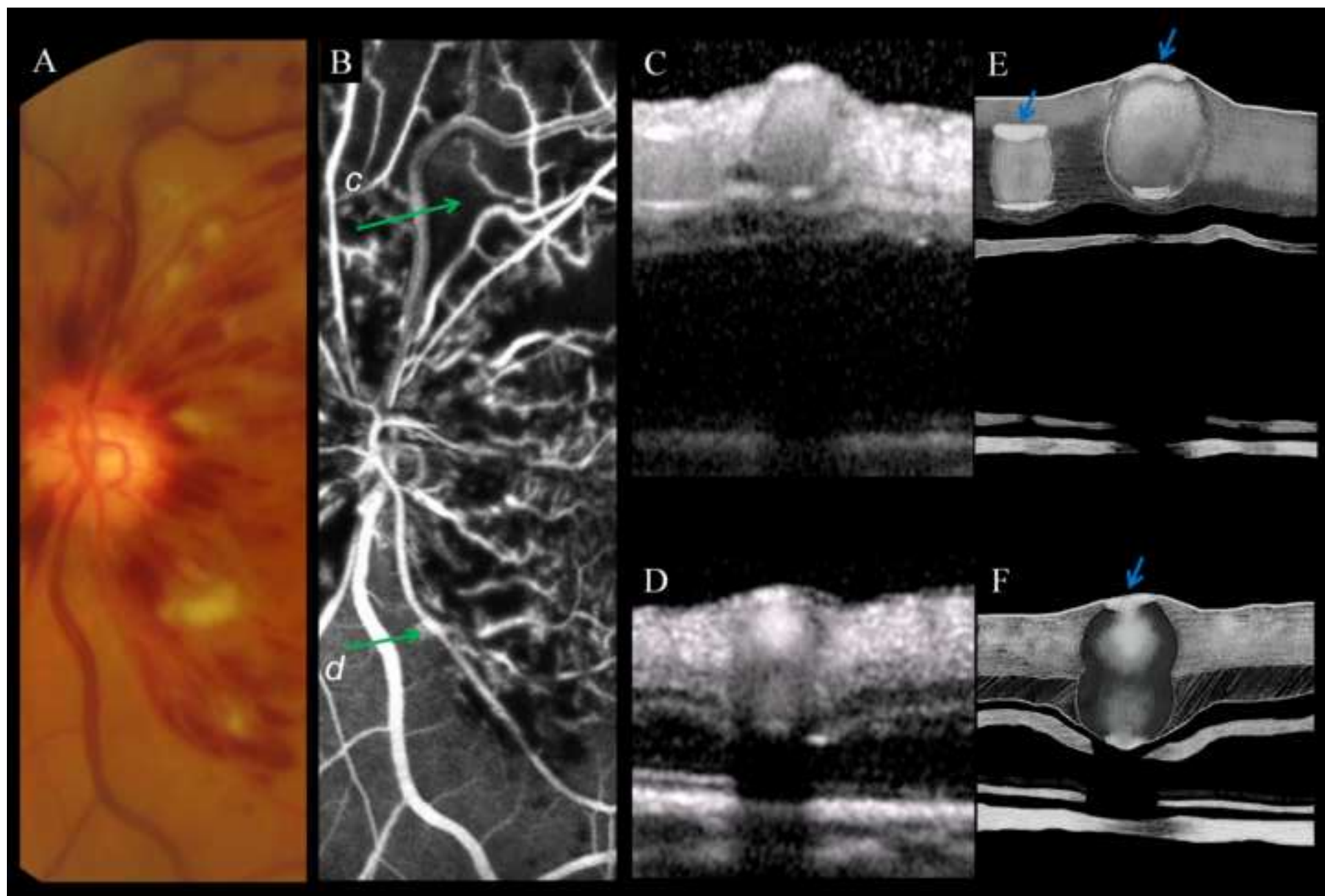
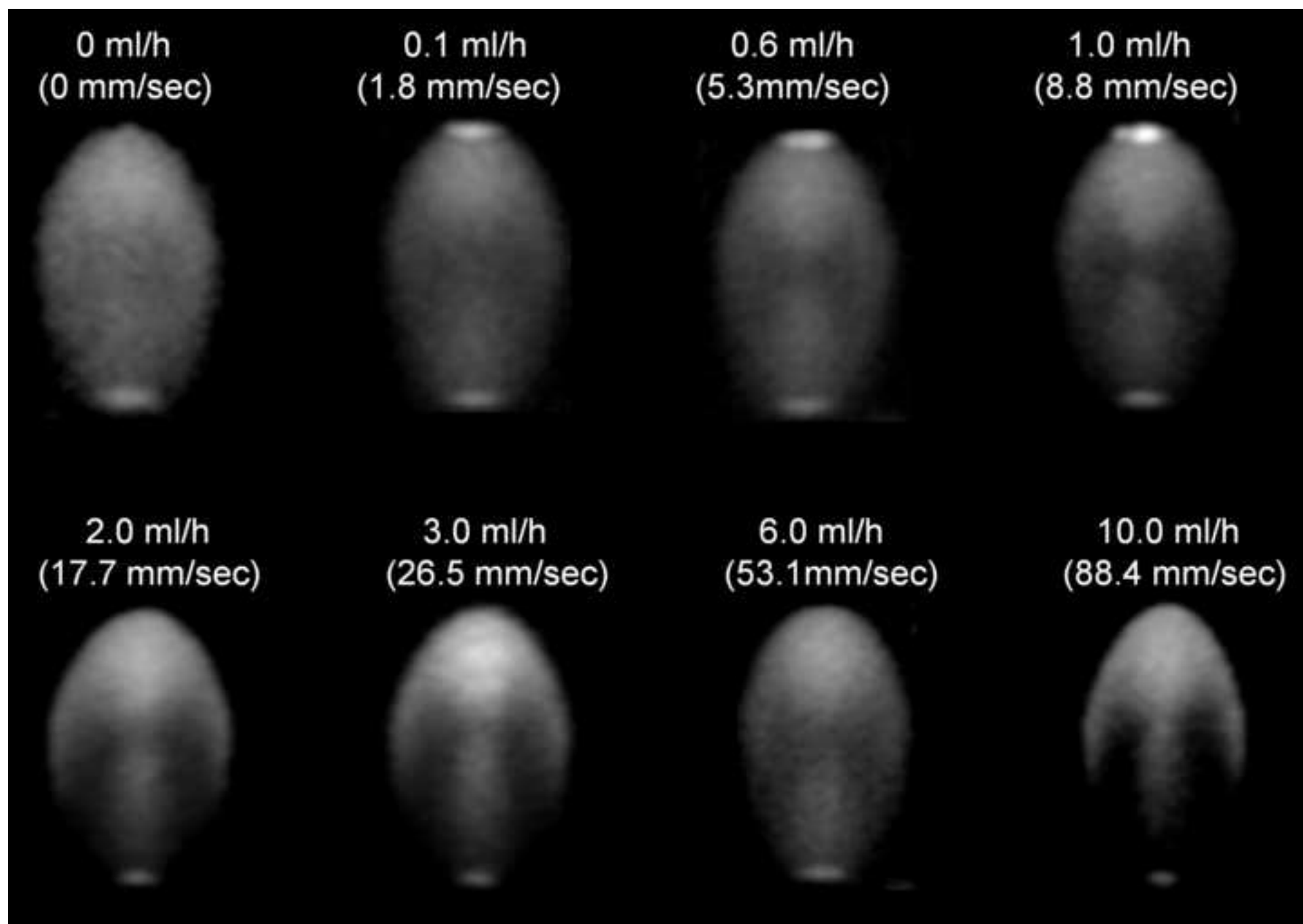
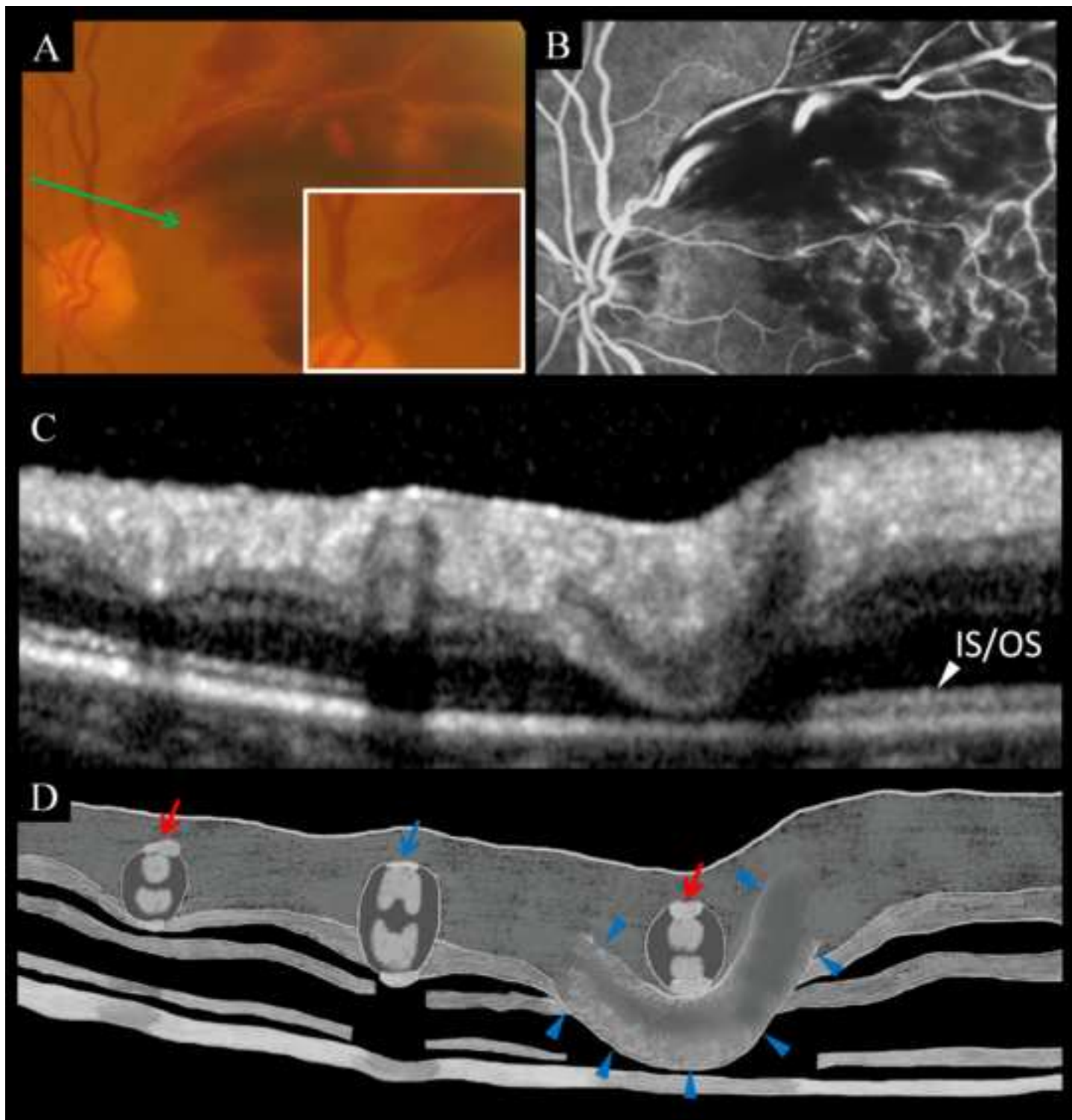


Figure5

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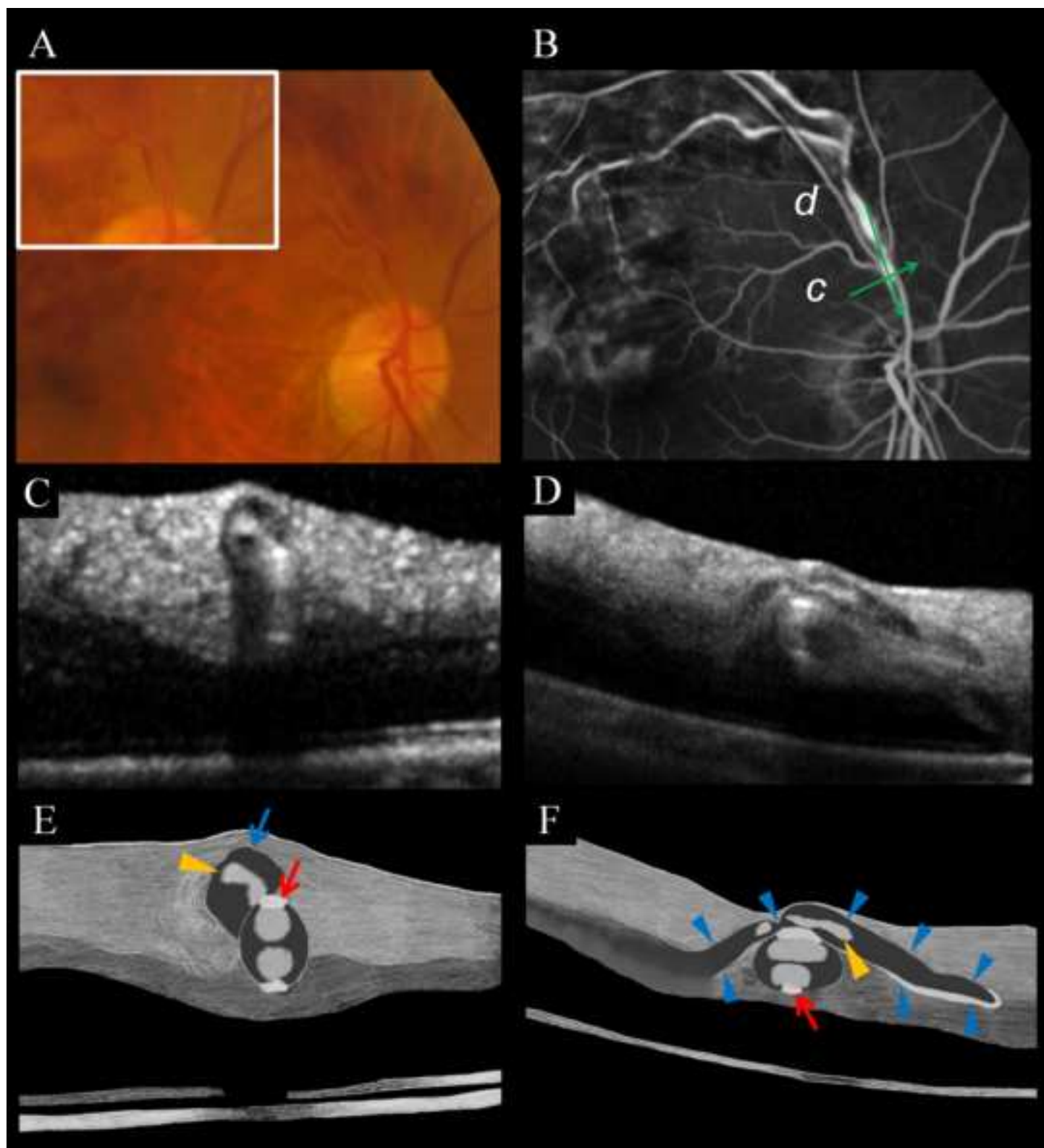
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Figure8

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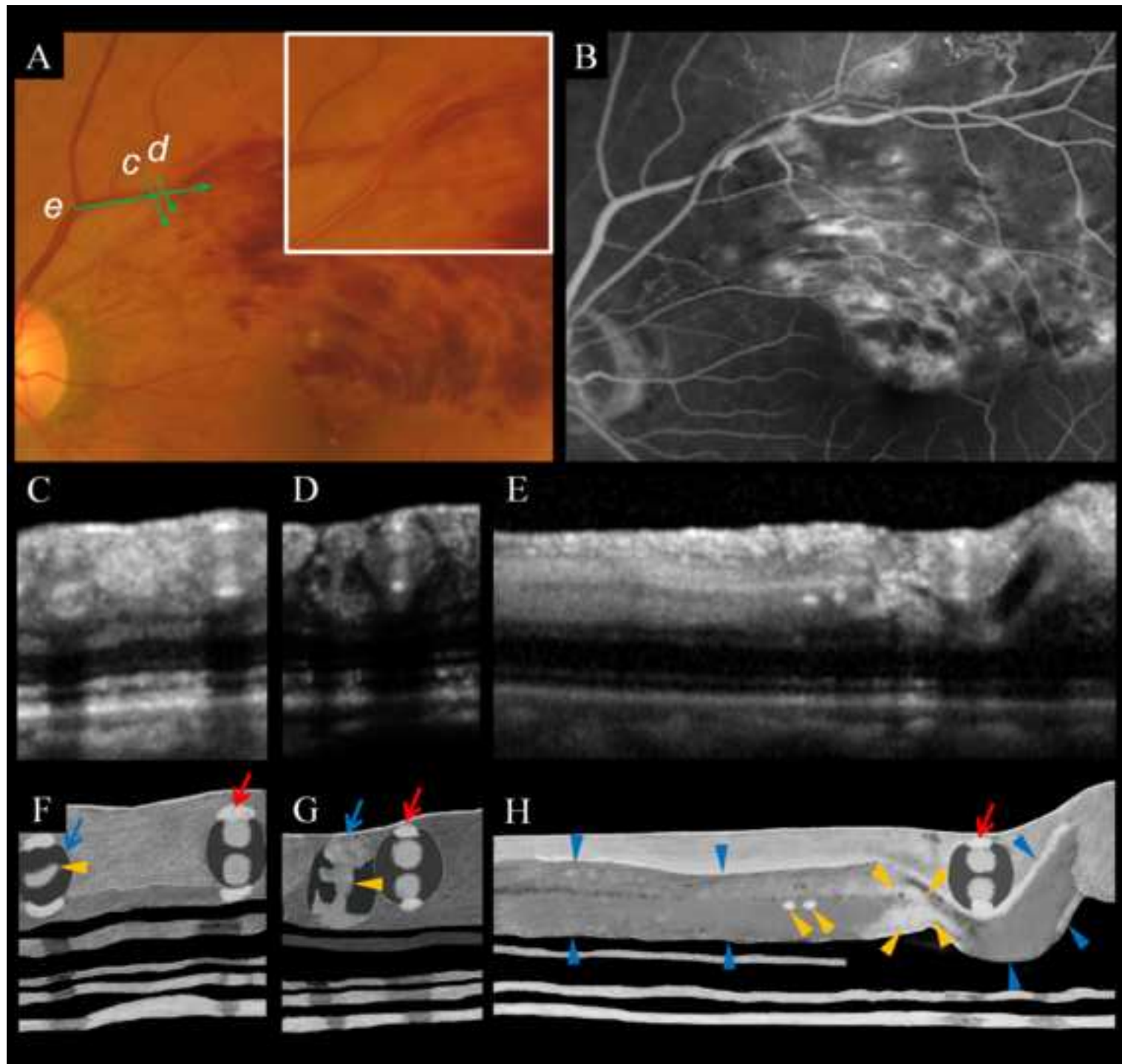


Figure legends

Figure 1. Cross-section of optical coherence tomography (OCT) in normal retinal

vessels. Fundus photograph (**A**) and infrared image (**B**) of an unaffected contralateral

5 eye. (**C**) An OCT image shows cross-sections of the retinal vessels along the green

arrow. Major retinal vessels are seen as oval-shaped configurations with 4 distinctive

hyperreflectivities. The top and bottom of the vessel walls show the innermost and

outermost hyperreflectivities. The reflectivity from the arterial walls is higher, compared

with that from venous walls. All retinal vessels with a physiological blood flow showed

10 inside hourglass-shaped hyperreflectivities. The internal paired hyperreflectivities show a

double “c” pattern in the convergent veins. (**D**) An illustration of Figure 1**C**. Red arrows

indicate arteries and blue arrows indicate veins.

Figure 2. Longitudinal section of optical coherence tomography (OCT) in normal retinal

15 vessels. Fundus photograph (**A**) and infrared image (**B**) of an unaffected contralateral

eye. OCT images along green arrows **c** and **d** show longitudinal sections of the major

retinal artery (**C**) and vein (**D**). Consistent with the cross-sections of the major retinal

vessels, retinal vessels show 4 hyperreflective bands. The innermost and outermost

bands are derived from the vessel walls, and the 2 intermediate bands are derived from the bloodstream. (E, F) Illustrations of Figure 2C and 2D. Red arrows indicate arteries and blue arrows indicate veins.

5 **Figure 3.** Optical coherence tomography (OCT) images of the retinal vein without blood flow. (A) Fundus photograph of a sheathed vein associated with old branch retinal vein occlusion. (B) Fluorescein angiogram shows no blood flow in the sheathed retinal vein. OCT images along green arrows **c** and **d** show a cross-section (C) and a longitudinal section (D) of the occluded retinal vein. Vessel lumen is totally hyperreflective. (E, F)

10 Illustrations of Figure 3C and 3D. Red arrows indicate arteries and blue arrows indicate veins.

Figure 4. Cross-sections of retinal veins with physiological and disturbed blood flow. Fundus photograph (A) and fluorescein angiogram (B) of an eye with hemi-central retinal

15 vein occlusion. Optical coherence tomography images along green arrows **c** and **d** show the cross-sections of the affected upper veins (C) and an unaffected lower vein (D). (C) Affected upper veins with disturbed blood flow show homogeneous internal reflectivity. (D) Unaffected lower vein with physiological blood shows innermost and outermost

hyperreflectivities from the venous wall and internal paired hyperreflectivities from blood flow. (E, F) Illustrations of Figure 4C and 4D. Blue arrows indicate veins.

Figure 5. Cross-sectional images of the blood flowing in the fine glass tube at different flow velocities obtained with Spectralis HRA+OCT. Cross-section of the blood within the glass tube without flow (at 0 mm/sec) shows homogeneous reflectivities. When the blood flow velocity was increased, the internal reflectivity became heterogeneous and hourglass-shaped hyperreflectivities were detected within the glass tube. At unphysiological blood flow velocity (88.4 mm/s), the internal reflectivity from the posterior part of the lumen disappeared.

Figure 6. Branch retinal vein occlusion at the arterial overcrossing. Fundus photograph (A) and fluorescein angiogram (B) of the branch retinal vein occlusion. Fluorescein angiogram confirms the arterial overcrossing at the affected crossing site. (C) Sectional image was obtained along the green arrow by using optical coherence tomography. The vein appears to run deep in the retinal layers below the overcrossing artery and appears to approach the junction between the inner and outer segments of the photoreceptor (IS/OS). The lumen of the vein at the crossing site is maintained. (D)

An illustration of Figure 6C. Red arrows indicate arteries and blue arrows indicate veins.

Figure 7. Branch retinal vein occlusion occurred at the venous overcrossing. Fundus photograph (A) and fluorescein angiogram (B) of branch retinal vein occlusion. (C, D)

5 Sectional image along green arrows **c** and **d** were obtained with optical coherence tomography. (C) Cross sectional image confirmed the venous overcrossing at the affected crossing site. (D) The retinal vein appears to be compressed and choked between the internal limiting membrane and the arterial wall at the crossing. A thrombus was seen within the lumen at the crossing site. (E, F) Illustrations of Figure
10 **7C** and **7D**. Red arrows indicate arteries and blue arrows indicate veins. Yellow arrows indicate the thrombus.

Figure 8. Thrombi within the vein affected with branch retinal vein occlusion. Fundus photograph (A) and fluorescein angiogram (B) of branch retinal vein occlusion. (C–E)

15 Sectional images along green arrows **c**, **d**, and **e** were obtained with optical coherence tomography. (C, D) Retinal artery at the crossing site shows a physiological appearance with internal paired hyperreflectivities. Retinal vein proximal to the affected crossing shows thrombus formation without physiological appearance. (E) Longitudinal section

of the retinal vein shows internal thrombus formation downstream of the affected crossing.

(E–G) Illustrations of Figure 8**C**, 8**D** and 8**E**. Red arrows indicate arteries and blue arrows indicate veins. Yellow arrows indicate thrombus.